08/418,870

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/418,870	04/07/95	VAN NEST	G 0085.006

18M1/1114

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EXAMINER	
AUER, H	
ART UNIT	**PAPER NUMBER**
1815	38

DATE MAILED: 11/14/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on Aug. 14, 1996.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-9, 29, and 36 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-9, 29 and 36 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

1. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1815.

2. Applicants' Amendment under 37 C.F.R. § 1.111, Paper No. 37, is acknowledged. Applicants have amended claim 1. Claims 1-9, 29, and 36 are pending.

3. Rejection of claims 1-9, 29 and 36 under 35 U.S.C. § 112, first paragraph is withdrawn. Applicants have disclosed the claimed invention in the specification as originally filed.

4. Rejection of claims 1-9, 29 and 36 under 35 U.S.C. § 112, second paragraph, is withdrawn, in view of the amendment to claim 1.

5. Rejection of claims 1, 5, 6, and 9 under 35 U.S.C. § 102(b) as being anticipated by Mizushima et al., U. S. Patent No. 4,613,505 is withdrawn, in view of the fact that Mizushima et al. disclose neither an adjuvant composition, nor any composition that has a biological activity free of their active agent.

6. Rejection of claims 1-9, 29 and 36 under 35 U.S.C. § 103 as being unpatentable over Hoskinson et al. in view of Mizushima et al., and further in view of Glass et al., is withdrawn in view of the failure of Mizushima et al. as a reference.

In their Amendment, Applicants allege that Hoskinson et al. does not teach oil adjuvants independently of a polycation in the aqueous phase. This assertion is overcome by the teaching in Hoskinson et al. that oil based adjuvants in conjunction with emulsifiers but without added mycobacteria have known immunoadjuvant properties (col. 2, l. 9-16; col. 3, l. 23-35). Hoskinson et al. combine these immunoadjuvant properties with the complementary properties known for polycations; it is to be emphasized that Hoskinson et al. do not teach a denial of immunoadjuvanticity for oil adjuvant emulsions. Also, it should be noted that muramyl peptides are derived from mycobacterial cell walls, so Hoskinson et al. by inference

suggests absence of muramyl peptides as well. Cationic polyelectrolytes, cited by Applicants in their traversal, are present in the aqueous phase.

Glass et al. is objected to as disclosing a composition wherein the oil component must be about 25% by volume with a maximum of 85%. Yet the disclosure of Glass et al. must be considered in its entirety for the disclosed invention as a whole. In use, the above adjuvant compositions of Glass et al. are diluted by further mixing with antigen suspensions (presumably aqueous) such that the final amounts of oil in the administered vaccine preparation fall within Applicants' limits. In Example VII (col. 15), if one supposes that the original adjuvant contained 50% oil, the dilutions encompassed in step 4 (90:10, or 75:25) yield final concentrations of oil of 5%, or 12.5%, respectively. In Example VIII, col. 19-20, the fourth column of the Table in col. 19 shows the final concentration of oil present in several vaccine formulations. All these fall within the range of 0.5 to 20% total volume (most preferred from 1-4%) of Applicants' adjuvant.

Applicants argue that the adjuvant of Glass et al.is intended to serve as a depot, and state that their own compositions do not serve as depots for antigen release. Yet Applicants immunized animals twice at a 1-month interval, and tested two weeks later (p. 51, l. 7-10), or thrice at 3-week intervals (p. 56, l. 28-31). Applicants have not demonstrated, as their Amendment avers on p. 14, that the antigen and the adjuvant is rapidly dispersed the site (sic) of introduction. It is respectfully noted that depot effects from Glass et al. and from Applicants are likely to be comparable.

NEW GROUNDS OF REJECTION

7. Claims 1-9, 29, and 36 are rejected under 35 U.S.C. § 103 as being unpatentable over Hoskinson et al. and Glass et al. in view of Idson (in Pharmaceutical Dosage Forms, Disperse Systems, Vol. 1, (Lieberman et al., eds.) Marcel Dekker, New York, 1988, pp. 199-243) (Idson), and Remington's Pharmaceutical Sciences ((Gennaro, ed.) Mack Publ. Co., Easton, PA, 1985, pp. 298-299, 317-329, and 1507-1511) (Remington).

As noted in the First Action, paper 35, Hoskinson et al. discloses an immunoadjuvant emulsion composition based on oils, including squalene, and Arlacel products including Arlacel A (mannide monooleate) or Arlacel 80, or Tween 80, as emulsifiers.

As noted in the First Action, paper 35, Glass et al. discloses an adjuvant preparation containing a combination of nonionic detergents, polyoxyethylene sorbitan monooleate and sorbitan monolaurate, in an o/w emulsion based on cottonseed oil.

In their Amendment, Paper 37, Applicants object to the use of Glass et al. as a reference. These arguments have been addressed and rebutted above, Item 6.

Idson teaches that immunoadjuvants based on W/O emulsions are known, and that there is considerable current interest in emulsified immunological preparations because of the slow release of the antigen (p. 224). Idson also reviews homogenization, including the valve and seat type of homogenizer (p. 229), such as the microfluidizer, and teaches that as the particle size of the internal phase decreases, the emulsion becomes more stable (p.233). In discussing stability of emulsions, Idson declares that reduction of particle size contributes greatly toward overcoming creaming (which leads to breaking of the emulsion), and notes that sizes below about 0.1 μm are difficult to attain (p. 237).

Remington teaches that microemulsions are frequently thermodynamically stable because, when formulated with both a surfactant and a cosurfactant the interfacial tension is greatly diminished (pp. 298-299). Stability of emulsions depends on many factors; among the most important is particle size (p. 327, col. 1-2). As the size diminishes the tendency for creaming is decreased, leading to greater stability of the emulsion. Remington discloses that homogenizers, in which the mixed phases are passed between a finely ground valve and seat under high pressure, are a known way to prepare emulsions (pp. 1510, col. 2-p. 1511, col. 1).

Thus Idson and Remington together teach the known advantage of microemulsions as having enhanced physical stability, and enable their preparation using homogenizers, for example.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare immunoadjuvant compositions based on O/W microemulsions in the absence of POP-POE block copolymers, and in the absence of any muramyl peptide, with a reasonable expectation of success, without undue experimentation, and without requiring the guidance of Applicants, because Hoskinson et al. discloses O/W emulsions in the absence of POP-POE block copolymers and in the absence of mycobacteria which are the source for muramyl peptides, because Glass et al. disclose a large number of emulsion systems, in the

absence of POP-POE block copolymers and in the absence of muramyl peptides, which upon dilution are used as immunoadjuvants, and because Idson and Remington motivate the art worker to employ microemulsions in applications including immunoadjuvants because of their known ability to increase the stability of the emulsion system. Further with regard to the absence muramyl peptides as a claim limitation, Applicants have stated in the Amendment, Paper 37, p. 6, that the presence or absence of muramyl peptides is not a critical feature of the present invention.

Applicants have submitted several printed publications in support their invention as part of their Amendment, Paper 37. The Amendment responds to other arguments in the Examiner's Action, Paper 35, by referring to these publications. The instant rejection on grounds of obviousness over Glass et al., and others, however, is not mitigated by evidence presented in these publications, since in order to do so, comparisons with formulations such as those of Glass et al. would need to have been presented. The closest that Applicants have come to doing so is in the Examples of the specification. As noted in Item 5 of the Examiner's Action, Paper 35, however, those results appear not to be sufficiently reproducible to present a preponderant case of the advantages of Applicants' invention over that of Glass et al. Thus Applicants fail to present a convincing case of nonobviousness.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group Art Unit 1815 Fax number is (703) 305-7939 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Henry E. Auer, Ph. D., whose telephone number is (703) 308-4240. The examiner can normally be reached Monday-Friday from 8:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marian Knode, can be reached on (703) 308-4311.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

HEA

Henry E. Auer, Ph. D.
November 8, 1996

MICHAEL P. WOODWARD
PRIMARY EXAMINER
GROUP 1800